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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,502	06/28/2006	Nicola Mary Aston	PB60197	8327

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EXAMINER	
KOSACK, JOSEPH R	

ART UNIT	PAPER NUMBER
1626	

NOTIFICATION DATE	DELIVERY MODE
09/04/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/551,502	ASTON ET AL.	
	Examiner	Art Unit	
	Joseph R. Kosack	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/30/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-12 and 15 are pending in the instant application.

Priority

The claim to priority as a 371 filing of PCT/EP04/03774 filed on April 7, 2004, which claims benefit of UK 0308186.6 filed on September 9, 2003 is acknowledged in the instant application.

Information Disclosure Statement

The Information Disclosure Statement filed on September 30, 2005 has been considered by the Examiner.

Claim Objections

Claim 9 is objected to because of the following informalities: referring to the specification for the scope of claimed subject matter. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12 and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for derivatives which are solvates in the solution phase, salts, and prodrugs of hydroxyl, amine, or carboxylic acid groups, does not reasonably provide enablement for derivatives which are solvates in the isolatable or solid form, other prodrugs, metabolites and residues. The specification does not enable

any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claims listed above are drawn not only to the compounds themselves, but also to solvates and hydrates thereof. The current skill in the art is that the existence and physical properties of isolatable or solid form solvates and hydrates is unpredictable. See Hildesheim et al., USPN 7,056,942, column 2, line 66 through column 3, line 5. Additionally, there are no examples present within the specification that teach a solid form solvate or hydrate. The term solvate as defined encompasses both solution-phase and isolatable solvates (pages 9-11 of the specification.) Therefore, on the virtue of the evidence above, it would require undue experimentation for one of skill in the art to make the solid and isolatable solvates that are claimed instantly. Additionally, no guidance is provided in how to make prodrugs of groups other than hydroxyl, amine, or carboxylic acid groups. Finally, the terms metabolite and residue are not defined, and no guidance is given to what compounds would be metabolites or residues of the genus of claim 1 or 15.

Claim 12 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating inflammation, does not reasonably provide enablement for other conditions mediated by p38 kinase activity or cytokines produced by the activity of p38 kinase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

.

The Nature of the Invention

The nature of the invention is to treat conditions mediated by p38 kinase activity or cytokines produced by the activity of p38 kinase.

The State of the Prior Art and the Predictability or Lack Thereof in the Art

The state of the prior art is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific disease). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The instant claimed invention is highly unpredictable as discussed below:
It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ

18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

Salituro et al. (*Current Medicinal Chemistry, 1999*, 807-823) show that a p38 inhibitor has been shown to treat inflammation in animal models and *in vitro* and *in vivo* testing. See pages 810-811. p38 is directly related to TNF-a and IL-1 which are cytokines associated with inflammation. Salituro et al. do detail other conditions that may be improved by inhibition of p38, however all of the additional conditions are related to inflammation. See pages 811-812.

Hence, in the absence of a showing of correlation between all diseases claimed as capable of treatment by the claimed compounds, one of skill in the art is unable to predict possible results from the administration of the compound of formula I except to treat inflammation due to the unpredictability of the role of those compounds in treating all other diseases, and the unpredictability of the ability of the compound of formula I to cause toxicity or any improvement in condition.

The Amount of Direction or Guidance Present and the Presence or Absence of Working Examples

The specification does show in vitro data of the some of the compounds to inhibit p38 with an IC50 of less than 10 uM, however no in vivo or animal model data is presented.

The Breadth of the Claims

The breadth of the claims is to treat all conditions mediated by p38 kinase activity or cytokines produced by the activity of p38 kinase.

The Quantity of Experimentation Needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine which other diseases can be treated with the compounds of the instant invention, dosages, the method of drug delivery, and any potential combination therapies.

The Level of Skill in the Art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compound of formula I for the treatment of all other possible diseases, other than inflammation, allegedly associated p38. As a result, necessitating one of skill to perform an exhaustive search for which cancers can be treated by what compounds of formula I in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001 , states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compound encompassed in the instant claims, with no assurance of success.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

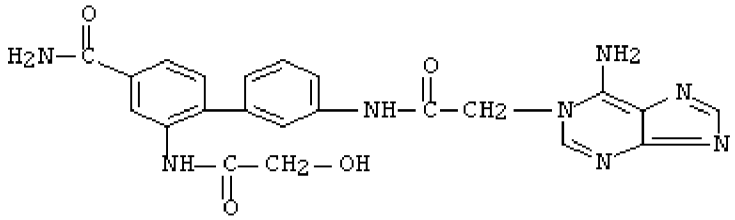
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4, 5, 7, 8, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jefferson et al. (WO 02/09648 A2).

Jefferson et al. teach the compound



, which corresponds to the claims wher R1 is hydrogen, m is 0, R2 is hydrogen, n is 1, Z is (CH2)sNHCOR16, s is 0, R16 is C1 alkyl substituted by 1 hydroxyl group, R3, X, and Y are hydrogen, R4 is -NH-CO-R7, R7 is (CH2)r-heteroaryl, and r is 1 as an antimicrobial compound. See compound 13 of Table 1, page 20.

Jefferson et al. do not teach where R3 is methyl instead of hydrogen.

The court in In re Wood, Whittaker, Stirling, and Ohta (199 USPQ 137) state that compounds with similar structures are expected to have similar properties unless there is evidence on the record of secondary considerations. Specifically, the court found that hydrogen and methyl are obvious variants for compound substitution and would be expected to have the same properties. Therefore, one of skill in the art would recognize that the compound of Jefferson et al. adequately suggests the instant compound where R3 is methyl.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-12 and 15 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-35 of copending Application No. 11/576,748. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are drawn to the same art specific subject matter.

The instant application and the '748 application have overlapping subject matter, especially where, in the instant application, Z is ortho to the other phenyl ring and is -(CH2)sCOOR16 or -(CH2)sCONR16R17 and R4 is CO-NH-(CH2)p-R8. Therefore, the '748 application would read the instant claims as compounds of the instant broad Markush group are also compounds of the narrower Markush group in the '748 application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Claims 1-12 and 15 are rejected. Claim 9 is objected to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph R. Kosack whose telephone number is (571)272-5575. The examiner can normally be reached on M-Th 6:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on (571)-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Golam M. M. Shameem, Ph.D./
Primary Examiner, Art Unit 1626

/Joseph R Kosack/

Examiner, Art Unit 1626